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**Keywords:** breast cancer; *BRCA1* and *BRCA2* genes; radiation-induced neoplasm; hereditary cancer; screening; costs/cost-effectiveness; simulation model

# Which screening strategy should be offered to women with *BRCA1* or *BRCA2* mutations? A simulation of comparative cost-effectiveness

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**Background:** There is no consensus on the most effective strategy (mammography or magnetic resonance imaging (MRI)) for screening women with *BRCA1* or *BRCA2* mutations. The effectiveness and cost-effectiveness of the Dutch, UK and US screening strategies, which involve mammography and MRI at different ages and intervals were evaluated in high-risk women with *BRCA1* or *BRCA2* mutations.

**Methods:** Into a validated simulation screening model, outcomes and cost parameters were integrated from published and cancer registry data. Main outcomes were life-years gained and incremental cost-effectiveness ratios. The simulation was situated in the Netherlands as well as in the United Kingdom, comparing the Dutch, UK and US strategies with the population screening as a reference. A discount rate of 3% was applied to both costs and health benefits.

**Results:** In terms of life-years gained, the strategies from least to most cost-effective were the UK, Dutch and US screening strategy, respectively. However, the differences were small. Applying the US strategy in the Netherlands, the costs were €43 800 and €68 800 for an additional life-year gained for *BRCA1* and *BRCA2*, respectively. At a threshold of €20 000 per life-year gained, implementing the US strategy in the Netherlands has a very low probability of being cost-effective. Stepping back to the less-effective UK strategy would save relatively little in costs and results in life-years lost. When implementing the screening strategies in the United Kingdom, the Dutch, as well as the US screening strategy have a high probability of being cost-effective.

**Conclusion:** From a cost-effectiveness perspective, the Dutch screening strategy is preferred for screening high-risk women in the Netherlands as well as in the United Kingdom.

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Women with a mutation in the *BRCA1* or *BRCA2* gene are at an increased lifetime breast cancer risk and they have a younger mean age at breast cancer diagnosis than that in the general population (mean age of onset: *BRCA1*, 53.9 years; *BRCA2*, 58.5 years; general population, 69.5 years) (Easton *et al*, 1995; Ford *et al*, 1998; Chen and Parmigiani 2007). These women are therefore offered mammography screening, which, in the general population, is the only screening test associated with reduced breast cancer mortality (Glasziou and Houssami 2011). However, mammography has reduced screening sensitivity in younger age groups (Yankaskas *et al*, 2010) and in gene mutation carriers (Warner *et al*, 2008). It has an increased risk of false-positive results at young age (Armstrong *et al*, 2007), which may cause distress and unnecessary biopsies, including surgical biopsy. It also gives an additional risk of radiation-induced tumours, which is particularly relevant in younger women (Preston *et al*, 2002; BEIR 7, 2006) and in those with cancer susceptibility genes (Jansen-van der Weide *et al*, 2010; Pijpe A *et al*, 2012).

The approach to overcome the above-noted limitations of mammography screening has been to use contrast-enhanced magnetic resonance imaging (MRI) to mammography for screening high-risk women, to increase the sensitivity of screening and to reduce the number of mammograms (Lord *et al*, 2007; Warner *et al*, 2008; Heijnsdijk *et al*, 2012). MRI has a higher sensitivity in this context than mammography and does not use ionising radiation. However, MRI has a variable sensitivity for ductal carcinoma *in situ*, generates higher costs and has a more limited availability and a lower specificity than mammography, which leads to more false positives in screening (Lord *et al*, 2007; Warner *et al*, 2008).

Recently, we published a validation study of the Simulation Model on Radiation Risk and breast cancer Screening (SiMRiSc), which quantified screening benefits and risks in various scenarios for women at an increased hereditary breast cancer risk (Greuter *et al*, 2010). The simulation model was shown to be valid and suitable for the provision of accurate benefits and risks estimates necessary for the refinement of screening guidelines in these women. The purpose of the present study is, therefore, to evaluate both the effectiveness and cost-effectiveness of existing breast cancer screening strategies in which MRI and mammography are used to screen women at an increased hereditary breast cancer risk with this simulation model.

## METHODS

**Description of the simulation model for screening.** We used the SiMRiSc model (Greuter *et al*, 2010; Lu *et al*, 2012) based on Jacobi *et al* (2006) and extended the model by incorporating data on the specificity of screening, on population death rates and on associated costs. In this micro-simulation model, women who had a chance of developing breast cancer and of death were followed up every year, based on probability functions. During the screening period, breast cancers were detected by mammography and/or MRI, based on the sensitivity of both modalities. In addition, during the screening period, breast cancers can develop and can clinically manifest between imaging. These are counted during the screening period as interval cancers. When a cancer is screen-detected or has become clinically manifested, costs of therapy and of hospital stay are calculated (see Description of the cost model). Women leave the simulation model when they die.

**The parameters of the model.** All values of the parameters that were used in the model were derived from literature (Table 1).

The tumour induction model consisted of the mean glandular dose for a two-view screen-film mammogram and the probability of tumour induction from radiation (BEIR 7, 2006; Zoetelief *et al*,

2006). The preclinical tumour growth model consisted of the mean and s.d. of the preclinical period based on the average tumour-doubling time of primary breast cancers in women younger than 50 years, in women between 50 and 70 years, and in those who were 70 years and older (Peer *et al*, 1993, 1996; Tilanus-Linthorst *et al*, 2007). The risk of developing breast cancer during life consisted of the baseline estimates for the lifetime risk of developing breast cancer for *BRCA1* and *BRCA2* mutation carriers (Easton *et al*, 1995; Ford *et al*, 1998). The sensitivity model consisted of mean sensitivities for film mammography and MRI; mean sensitivity of mammography was for five age groups (Kriege *et al*, 2006; Kerlikowske *et al*, 2000), whereas mean sensitivity of MRI was an overall sensitivity, as it was independent of age (Warner *et al*, 2008).

The specificity model consisted of the mean specificities for each of mammography and MRI; mean specificity of mammography was for women younger (or older) than 40 years of age (Kriege *et al*, 2006) and mean MRI specificity was an overall specificity that was independent of age (Warner *et al*, 2008). The population death-rate model consisted of the cumulative death rates at ages up to 100 years, based on the Dutch cohort who were born in 1970 ([www.statline.cbs.nl](http://www.statline.cbs.nl)). The breast cancer death risk consisted of the probability of death from breast cancer that was linked to the tumour volume according to the preclinical tumour growth model ([www.cijfersoverkanker.nl](http://www.cijfersoverkanker.nl)).

**Description of the cost model.** Cost parameters included the direct costs of screening, diagnostics, therapy and hospital stay (Table 2). Costs of screening included that of mammography examination and/or an MRI examination. Costs of diagnostics included the costs of biopsy and of histopathological analysis. Costs of therapy included costs of surgical, chemotherapeutic endocrine and/or radiotherapeutic treatment. The costs were estimated for the Netherlands and for United Kingdom separately. For the calculation of the costs in the Netherlands, the unit prices for screening, diagnostics and therapy were based on current national tariffs and the Dutch published studies on cost prices ([www.cvz.nl](http://www.cvz.nl); Flobbe *et al*, 2004; LPRM and NABON, 2000; Farmacotherapeutisch Kompas, 2000/2001; Slotman *et al*, 2000; Oostenbrink *et al*, 2000). For the calculation of costs in the UK scenario, data were based on national tariffs and the UK studies on cost prices (NICE, 2006; Prescott *et al*, 2007). Mean treatment costs per patient were calculated by combining prices and treatment data from the Dutch regional cancer registry, stratified by tumour size (Table 3).

**Validation of the model.** The SiMRiSc model was validated by comparing model-predicted outcome data with observed data from three published large screening studies of women with an increased hereditary breast cancer risk (Greuter *et al*, 2010). A sensitivity analysis was used to estimate the error margins of model-predicted outcome data and to analyse the sensitivity of the simulation model to each input parameter. It was shown that the model predicted the number of tumours reported to a high accuracy. The model was the most sensitive to changes in the parameters related to the lifetime breast cancer risk and the sensitivity of mammography.

**Screening strategies.** Three existing screening strategies were evaluated (Table 4). The Dutch strategy uses an annual MRI analysis for women aged 25–30 years, annual mammography and MRI for those aged 30–60 years and a biennial mammography-only for those aged 60–75 years ([www.cbo.nl](http://www.cbo.nl)). The UK strategy uses an annual mammography and MRI analysis for women aged 30–50 years and a mammography-only for those aged 50–70 years for every 3 years ([www.nice.org.uk](http://www.nice.org.uk)). The US strategy includes an annual mammography and MRI analysis for women aged 25 years until the end of life, according to the American Cancer Society guidelines and the National Comprehensive Cancer Network

Table 1. Parameters of the screening model.

Model component	Parameter	Baseline estimate	Minimum estimate	Maximum estimate	Reference
Tumour induction due to radiation risk	Dose (mSv)	3	1	5	Peer <i>et al</i> (1993)
	The lifetime probability of tumour induction	0.51	0.28	0.83	Preston <i>et al</i> (2002)
Preclinical tumour growth	Mean preclinical period (years)				
	< 50 years	1.9	0.63	3.17	Peer <i>et al</i> (1996); Tilanus-Linthorst <i>et al</i> (2007); Kriege <i>et al</i> (2006)
	50–70 years	3.7	1.23	6.17	
	> 70 years	4.5	1.50	7.50	
	s.d. (years)				
	< 50 years	0.63	0.21	1.05	(Peer <i>et al</i> , 1996; Tilanus-Linthorst <i>et al</i> , 2007; Kriege <i>et al</i> , 2006)
	50–70 years	0.51	0.17	0.85	
	> 70 years	1.06	0.35	1.77	
	Tumour-doubling times (days)				
	< 50 years	80	27	133	Peer <i>et al</i> (1996); Tilanus-Linthorst <i>et al</i> (2007); Kriege <i>et al</i> (2006)
	50–70 years	157	52	262	
	> 70 years	188	63	313	
Risk of developing breast during life	BRCA1 probability function				
	Lifetime risk at age 70 years	0.80	0.71	0.84	Easton <i>et al</i> (1995); Ford <i>et al</i> (1998)
	Mean age (years)	53.9	43.9	63.9	
	s.d. (years)	16.5	5.5	28	
	BRCA2 probability function				
	Lifetime risk at age 70 years	0.76	0.69	0.76 <sup>a</sup>	Easton <i>et al</i> (1995); Ford <i>et al</i> (1998)
	Mean age (years)	58.5	48.5	68.5	
	s.d. (years)	13.8	4.6	23	
Sensitivity	Sensitivity of mammography at age < 40 years	0.333	0.279	0.397	Kerlikowske <i>et al</i> (2000)
	Sensitivity of mammography at age 40–49 years	0.389	0.326	0.464	
	Sensitivity of mammography at age 50–54	0.556	0.466	0.663	
	Sensitivity of mammography at age 55–59 years	0.697	0.584	0.832	Warner <i>et al</i> (2008)
	Sensitivity of mammography at age ≥ 60 years	0.838	0.702	1	
	Sensitivity of MRI for all age groups	0.770	0.593	1	
Specificity	Specificity of mammography at age < 40 years	0.961	0.924	1	Kerlikowske <i>et al</i> (2000)
	Specificity of mammography at age ≥ 40 years	0.946	0.909	0.984	Warner <i>et al</i> (2008)
	Specificity of MRI for all age groups	0.863	0.745	1	
Death rate	Average life expectancy population (years)	79	—	—	www.RIVM.nl www.cijfersoverkanker.nl
	5-year survival rate breast cancer patients				
	Tumour diameter < 20 mm	0.98	—	—	
	Tumour diameter 20–50 mm	0.86	—	—	
	Tumour diameter > 50 mm	0.62	—	—	

Minimum and maximum estimates correspond with two times the s.d. For a detailed description of the parameters, see Heijnsdijk *et al* (2012).

<sup>a</sup>The maximum estimate is equal to the baseline estimate because the lifetime risk at the age of 100 years is 100%.

guidelines (Saslow *et al*, 2007; www.NCCN.org). When the strategy in the model recommended a mammography and an MRI analysis, these techniques were performed sequentially: first, mammography was performed and, if positive, a screen-detected breast cancer was counted. If the mammography was negative, an MRI was subsequently performed.

**Input population.** The input population consisted of a cohort of 10 000 women followed since the age of 20 years. On the basis of the lifetime probability function for breast cancer given the woman's specific gene mutation and age (Easton *et al*, 1995; Ford *et al*, 1998), breast cancers were distributed randomly over the simulated population each year. Each year, the age of the women

was increased, existing tumours were allowed to grow based on age (Peer *et al*, 1993, 1996; Tilanus-Linthorst *et al*, 2007), women died as based on a probability function (www.rivm.nl) and, during screening, growing breast cancers could be detected by mammography and/or MRI scanning based on the sensitivity of both modalities and the screening strategy of the specific country (Kerlikowske *et al*, 2000; Kriege *et al*, 2006; Yankaskas *et al*, 2010).

**Analysis and model output.** The output of the model (Tables 5a and b) was given in terms of the absolute number of small tumours (diameter < 2 cm) detected, the number of tumours detected with mammography or MRI screening, the number of

**Table 2.** Resource items for screening, diagnostics and treatment: unit prices for the Netherlands and the United Kingdom, and sources

Cost category	Unit price € (The Netherlands)	Source	Unit price £ (United Kingdom)	Source/HRG code
<b>Screening</b>				
Mammography (National Breast Screening Program)	69	www.cvz.nl	46	www.whnt.nhs.uk
Mammography (hospital)	92	www.cvz.nl	58	NICE (2006)
MRI	227	www.cvz.nl	220	Prescott <i>et al</i> (2007)
<b>Diagnostics</b>				
Pathology and evaluation	75	Flobbe <i>et al</i> (2004)	122	Prescott <i>et al</i> (2007)
<b>Treatment</b>				
Breast conserving therapy	1009	www.cvz.nl	808	<sup>a</sup>
Mastectomy	1856	www.cvz.nl	2549	HRG J11
Radiation therapy	2891	Flobbe <i>et al</i> (2004); LPRM and NABON (2000); Slotman <i>et al</i> (2000)	2316	<sup>a</sup>
Chemo therapy	950	Flobbe <i>et al</i> (2004); Slotman <i>et al</i> (2000)	761	<sup>a</sup>
Hormonal therapy	733	Flobbe <i>et al</i> (2004); Slotman <i>et al</i> (2000)	587	<sup>a</sup>
Specialist visits	672	Flobbe <i>et al</i> (2004)	538	<sup>a</sup>
Specialist visits (adjuvant therapy)	1788	Flobbe <i>et al</i> (2004)	1433	<sup>a</sup>
Hospital stay	1594	Flobbe <i>et al</i> (2004); Oostenbrink <i>et al</i> (2000)	1277	<sup>a</sup>

Abbreviation: HRG = Healthcare Research Group.

<sup>a</sup>If there was no HRG code, prices calculated were based on the balance between the per capita expenditures of the Netherlands vs that of the United Kingdom (0.84) (stats.oecd.org, visited online: June 2012) and the conversion rate on 1 January 2009, which is 0.96 for UK pounds (www.x-rates.com visited online: June 2012).**Table 3.** Mean treatment costs per patient by tumour size

	≤ 2 cm		> 2 cm and ≤ 5 cm		> 5 cm	
	Costs €	Costs £	Costs €	Costs £	Costs €	Costs £
Total therapy	4268	3909	4812	4105	5426	4789
Hospital stay	1589	1273	1573	1260	1580	1266
Total	5857	5182	6485	5365	7006	6055

interval cancers, the number of tumours diagnosed before the start of screening and those after commencing the screening, the number of mammography examinations (within the hospital and within the National Breast Cancer Screening Program), the number of MRI examinations and the number of false positives for mammography and MRI. We calculated the life-years gained by high-risk screening, the costs of this screening and the incremental cost-effectiveness rate (ICER) defined as the ratio of the additional costs per life-year gained, where the national strategy was the reference. The simulation was run for the two gene types separately. In the analyses, a discount rate of 3% per year was applied to costs and life-years from 20 years of age.

The simulation was carried out in the Netherlands, comparing the three screening strategies with the Dutch population screening as a reference, and a cost threshold of €20 000 was considered (Habbema *et al*, 1989). As the population screening was the reference and this differs over countries, in a second analysis the simulation was carried out in the United Kingdom and the British population screening was used as a reference. In this analysis, a cost threshold of £25 000 was considered (National Institute for Health and Clinical Excellence, 2007).

**Sensitivity analysis.** A probabilistic sensitivity analysis (PSA) was performed for the ICER outcome. In 100 simulations, each consisting of 1000 women, the input parameters of the model were randomly selected from a skewed Gaussian distribution, with a mean equal to the parameter's baseline estimate and a negative s.d. equal to half the difference between the mean and the minimum estimate, and with a positive s.d. equal to half the difference between the maximum and the mean estimate (Table 1). On the basis of the outputs of the PSA, cost-effectiveness acceptability curves were constructed (Matchar *et al*, 2005).

## RESULTS

Table 5a summarises model outputs stratified for *BRCA1* and *BRCA2* for all three screening strategies when implemented in the Netherlands, whereas Table 5b summarises model outputs for all three screening strategies when implemented in the United Kingdom. The earlier the screening started (the Dutch and US strategies), the higher the number of small tumours (<2 cm) that was detected (Table 5a). This effect was most pronounced among the women with a *BRCA1* or *BRCA2* mutation. In addition, the earlier the screening started, the lower the number of tumours that was diagnosed before commencing the screening; this was most pronounced among women with a *BRCA1* mutation.

The longer the screening was continued (the US strategy offers the longest time for continuing screening), the more the tumours were diagnosed. The longer the screening was offered, the smaller the number of tumours that was diagnosed after stopping the screening. More frequent MRI screens (the US strategy offers the most frequent MRI screens) resulted in less interval cancers. The numbers of false positives for mammography screening and for MRI screening were highest in the US strategy and were lowest in the UK strategy for all groups.



Table 4. Evaluated screening strategies for breast cancer in women with a *BRCA1/2* mutation

Age (years)	Dutch strategy	UK strategy	US strategy
25–30	MRI every year	No screening	MRI and mammography every year
30–50	MRI and mammography every year	MRI and mammography every year	MRI and mammography every year
50–60	MRI and mammography every year	Mammography every 3 years in NBSP	MRI and mammography every year
60–70	Mammography every 2 years in NBSP	Mammography every 3 years in NBSP	MRI and mammography every year
70–75	Mammography every 2 years in NBSP	No screening	MRI and mammography every year
Age over 75 when being in good health	No screening	No screening	MRI and mammography every year

Abbreviation: NBSP = National Breast Cancer Screening Program.

Table 5a. Comparison of the Dutch screening strategy as implemented in NL

Genetic mutation	<i>BRCA1</i>			<i>BRCA2</i>		
Screening strategy	NL	UK	US	NL	UK	US
Small tumours detected (<2 cm)	750 ± 11	663 ± 15	799 ± 11	777 ± 12	696 ± 11	821 ± 13
Tumours detected	791 ± 23	717 ± 22	838 ± 24	814 ± 17	749 ± 15	851 ± 18
Interval cancers	88 ± 11	153 ± 12	59 ± 6	61 ± 5	119 ± 9	32 ± 5
Tumours diagnosed before start of screening	42 ± 6	73 ± 11	43 ± 7	16 ± 3	36 ± 5	17 ± 4
Tumours diagnosed after end of screening	26 ± 6	30 ± 5	N.A.	27 ± 5	30 ± 4	N.A.
Mammography examinations in hospital (× 1000)	18.9 ± 0.5	15.2 ± 0.4	24.5 ± 0.4	21.1 ± 0.3	16.7 ± 0.2	27.4 ± 0.3
Mammography examinations in NBSP (× 1000)	1.0 ± 0.1	3.2 ± 0.2	N.A.	1.2 ± 0.1	3.9 ± 0.1	N.A.
MRI examinations (× 1000)	23.2 ± 0.5	15.1 ± 0.2	23.9 ± 0.3	25.6 ± 0.3	16.6 ± 0.1	26.8 ± 0.3
False-positive mammographies	904 ± 36	831 ± 30	1.081 ± 28	1.033 ± 46	939 ± 34	1.231 ± 38
False-positive MRIs	3.139 ± 86	2.033 ± 48	3.231 ± 71	3.448 ± 38	2.249 ± 40	3.624 ± 74
Years of life gained (years/woman) <sup>a</sup>	1.614	1.366	1.620	1.217	1.077	1.221
Additional costs (× €1000 per woman) <sup>b</sup>	2.292	1.572	2.555	2.511	1.743	2.786
Additional costs per life-year gained compared with NL strategy (× €1000 per year per woman)	—	2.9 <sup>c</sup>	43.8	—	5.5 <sup>c</sup>	68.8

Abbreviations: MRI = magnetic resonance imaging; N.A. = not applicable; NBSP = National Breast Cancer Screening Program; NL = The Netherlands Comparison of the Dutch screening strategy as implemented in NL, with the British (UK) and American (US) screening strategy when implemented in NL, assuming simultaneous application of the Dutch NBSP. Average values of absolute numbers ± s.d. per 1000 women with a *BRCA1* or *BRCA2* genetic mutation.

<sup>a</sup>Reference is Dutch NBSP.

<sup>b</sup>Additional costs with reference to Dutch NBSP, all cost estimates based on Dutch prices.

<sup>c</sup>Savings: programme is less expensive and adds less life-years gained with respect to the Dutch strategy.

When applying the US strategy in the Netherlands, €43 800 and €68 800 should be paid for an additional life-year gained for *BRCA1* and *BRCA2*, respectively (Table 5a). At a threshold of €20 000 per life-year gained, implementing the US strategy in the Netherlands has a very low probability of being cost-effective. However, if the Dutch are willing to pay €50 000 per life-year gained, then the US strategy has a more than 80% probability of being cost-effective (see Figure 1A). Stepping back to the less-effective UK strategy would save relatively little in costs and result in life-years lost. The ICERs are a few thousand euros per life-year gained, indicating that the Dutch strategy is cost-effective compared with the UK strategy.

When the simulation was carried out in the United Kingdom, the US screening strategy was somewhat more effective for estimates of life-years gained as compared with the Dutch strategy (Table 5b). Both the US and the Dutch screening strategy were more effective for estimates of life-years gained as compared with the UK strategy. When applying the Dutch strategy in the United Kingdom, £2700 and 4900 should be paid for an additional

life-year gained for *BRCA1* and *BRCA2*, respectively (Table 5b). Turning to the even more intensive US strategy in the United Kingdom would cost an additional £3400 and 6200 per life-year gained (Table 5b). Thus, at current UK thresholds, the Dutch and the US strategy are an extension with additional costs per QALY that have a high (100%) probability of falling below the UK threshold (see Figures 1B and C).

## DISCUSSION

Differences between the currently recommended screening strategies for women at high risk of developing breast cancer reflects the uncertainties surrounding the optimal screening commencement (and stopping) age, duration and frequency of screening, and the schedule for integrating mammography and MRI screening. Using simulation modelling, we found that the US screening strategy showed a small increase in the number of life-years gained

Table 5b. Comparison of the UK's screening strategy as implemented in the United Kingdom

Genetic mutation	<i>BRCA1</i>			<i>BRCA2</i>		
Screening strategy	NL	UK	US	NL	UK	US
Small tumours detected (< 2 cm)	684 ± 12	552 ± 18	748 ± 11	670 ± 12	545 ± 15	755 ± 9
Tumours detected	731 ± 21	624 ± 18	781 ± 25	715 ± 16	618 ± 21	781 ± 16
Interval cancers	144 ± 13	241 ± 14	114 ± 9	146 ± 13	241 ± 15	101 ± 10
Tumours diagnosed before start of screening	37 ± 8	76 ± 8	41 ± 7	16 ± 4	37 ± 6	17 ± 4
Tumours diagnosed after end of screening	83 ± 8	100 ± 10	54 ± 5	110 ± 13	129 ± 7	64 ± 9
Mammography examinations in hospital (× 1000)	19.0 ± 0.4	15.2 ± 0.1	24.7 ± 0.3	21.1 ± 0.3	16.6 ± 0.2	27.4 ± 0.4
Mammography examinations in NBSP (× 1000)	0.7 ± 0.1	2.2 ± 0.1	N.A.	0.9 ± 0.1	2.7 ± 0.1	N.A.
MRI examinations (× 1000)	23.4 ± 0.4	15.1 ± 0.1	24.2 ± 0.3	25.7 ± 0.3	16.5 ± 0.2	26.8 ± 0.4
False-positive mammographies	909 ± 21	778 ± 25	1.097 ± 21	1.015 ± 33	871 ± 27	1.222 ± 33
False-positive MRIs	3.134 ± 79	2.035 ± 28	3.273 ± 62	3.457 ± 59	2.245 ± 49	3.624 ± 77
Years of life gained (years per woman) <sup>a</sup>	1.625	1.368	1.628	1.231	1.077	1.231
Additional costs (× 1000 per woman) <sup>b</sup>	2.153	1.454	2.350	2.339	1.588	2.550
Additional costs per life-year gained compared with the UK strategy (× 1000 per year per woman)	2.7	—	3.4	4.9	—	6.2

Abbreviations: MRI = magnetic resonance imaging; N.A. = not applicable; NBSP = National Breast Cancer Screening Program; NL = The Netherlands. Comparison of the UK's screening strategy as implemented in the United Kingdom with the Dutch (NL) and American (US) screening strategy when implemented in the United Kingdom, assuming simultaneous application of the UK NBSP. Average values of absolute numbers ± s.d. per 1000 women with a *BRCA1* or *BRCA2* genetic mutation.

<sup>a</sup>Reference is British NBSP.

<sup>b</sup>Additional costs with reference to British NBSP, all cost estimates based on British prices.

compared with the Dutch strategy, and both the US and the Dutch screening strategies were more effective in terms of life-years gained compared with the UK strategy. Applying the US strategy in the Netherlands would cost €43 800 and 68 800 for an additional life-year gained for *BRCA1* and *BRCA2*, respectively. The cost-effectiveness acceptability curves confirm that the Dutch strategy seems the most cost-effective option.

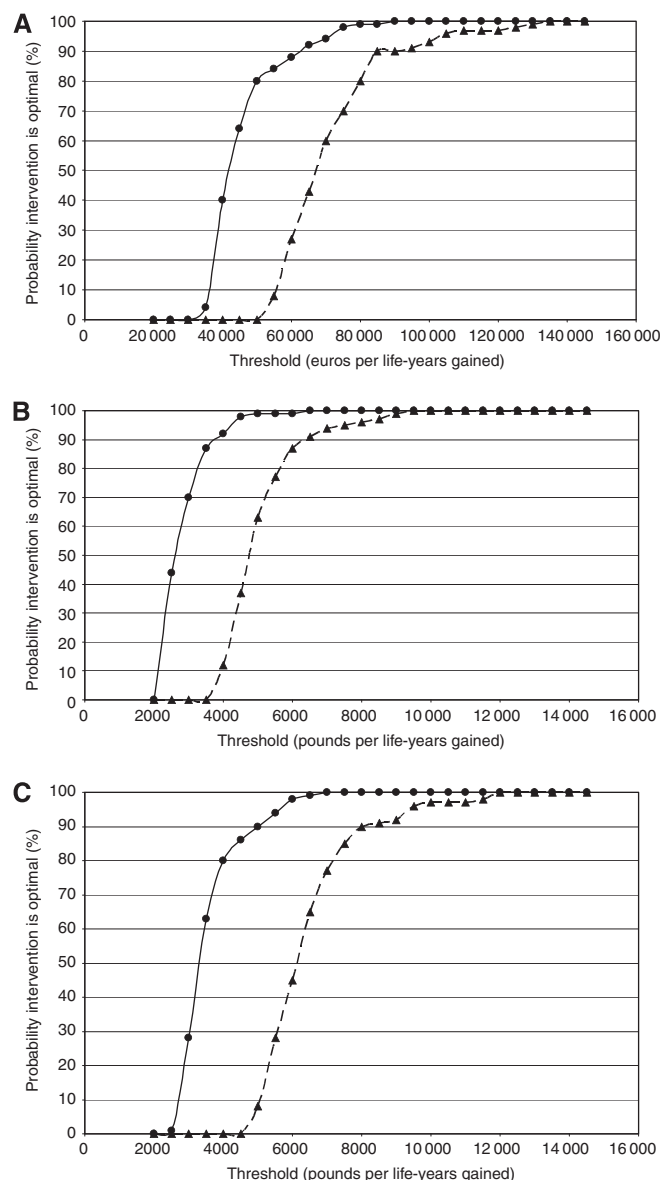
Screening *BRCA1* mutation carriers was more cost-effective than screening *BRCA2* mutation carriers. This may be partly explained by the higher lifetime risk of breast cancer in *BRCA1* mutation carriers than *BRCA2* mutation carriers, 0.80 and 0.76 by age 70 years, respectively, as well as the lower mean age of onset in *BRCA1* mutation carriers, 53.9 vs 58.5 years, respectively (Chen and Parmigiani, 2007; Van der Kolk *et al*, 2010). Because of the higher incidence and the lower mean age of breast cancer among *BRCA1* mutation carriers, more women with *BRCA1* mutations are expected to die of breast cancer and, hence, there may be greater potential for life-years gained by screening this group (Kurain *et al*, 2010).

For *BRCA1* and *BRCA2* mutation carriers in the Netherlands, the Dutch screening strategy, starting MRI-only screening at age 25 years, was most cost-effective (Table 5a). The US strategy, which combines MRI scanning and mammography from the age of 25 years, gave only a small increase in the number of life-years gained relative to the Dutch strategy, and a slight reduction in interval cancers. A likely explanation for this finding is that the sensitivity of screening mammography in women between age 25 and 30 years is relatively low, that is, 0.333 (Johnstone *et al*, 2001). Hence, mammography between age 25 and 30 years does not increase benefit over commencing with MRI-alone screening from 25–30 years (Heijnsdijk *et al*, 2012). The small increase in the number of life-years gained through screening in the US strategy relative to the Dutch strategy might also be an effect of radiation-induced tumours; the estimated additional amount of induced breast tumours was 0.6% (Jansen-van der Weide *et al*, 2010; Pijpe *et al*, 2012). Of note, the longer duration of screening with MRI in the

US strategy considerably increases screening costs and false-positive screens relative to the Dutch and UK strategies, which reduces the cost-effectiveness of screening.

The strengths of the modelling reported in this work include the construct of model parameter values, which were mostly derived from publications concerning women with *BRCA1* or *BRCA2* mutations. Furthermore, the model was applied to currently applied guideline-based screening scenarios, and included the effects of MRI and of X-ray tumour induction, as well as cost analysis, to guide selection of the most cost-effective screening strategy. Importantly, we considered costs of screening, as well as costs of treatment (stratified for tumour size) and hospital stay, whereas most studies on this topic limit their scope to costs of screening. In addition, the costs included in this analysis were based on a detailed country-specific cost study of the prices for diagnostics and treatment of early-stage breast cancer, and a discount rate was applied to costs and life-years.

Estimates for the costs of advanced breast cancer, including distant metastases, diagnostics and treatment, were not included in the current model. For this reason, we think that this model underestimates the costs of breast cancer treatment, which will be a problem when the model is applied to assess the overall cost-effectiveness of the breast cancer screening in high-risk women, rather than choosing which strategy is best. Furthermore, as the main focus of the present paper was to study the cost-effectiveness comparing the different strategies situated in the Netherlands or in the United Kingdom, the US prices were not used. If the simulation had been carried out in the United States, the fact that the per capita health-care expenditures are about 2.05 times higher in the United States has to be taken into account (stats.oecd.org). Another limitation is that we did not incorporate quality-of-life parameters that may be relevant in breast cancer screening, in line with the work of Rijnsburger *et al* (2004), suggesting that there is no loss of quality of life due to screening in high-risk women. Although we did not consider quality-of-life parameters to be in the scope of the present work, it represents an important topic for



**Figure 1.** Cost-effectiveness acceptability curves. Cost-effectiveness acceptability curves for the implementation of the US screening strategy in the Netherlands (**A**), of the Dutch screening strategy in the United Kingdom (**B**) and of the US screening strategy in the United Kingdom (**C**) for *BRCA1* (solid line, circles) and *BRCA2* (dashed line, triangles) mutation carriers. Shown is the probability that the alternative intervention is cost effective at a certain cost threshold in euros or pounds per life-years gained.

further research. A further limitation might be that screening vs clinical detection was not directly but indirectly included by assuming breast cancer mortality to be dependent on tumour volume. In addition, the dose and the sensitivity were based on film mammography, although current clinical practice includes digital mammography, which has a lower dose, and digital mammography is more accurate in women under 50 years and in pre-menopausal women (Pisano *et al*, 2005). However, as in the population screening programme most screenings are captured on a film, we modelled the film mammography. A related potential limitation is that additional sensitivity analyses, such as two-way sensitivity analysis of diagnostic test performance, were not performed. However, we learned from previous analyses that penetrance was the most influential factor in this model

(Greuter *et al*, 2010); hence, analyses including a lower dose and additional sensitivity analyses are unlikely to alter our findings. An inherent limitation of simulation modelling is that some of the included parameters are associated with uncertainty—in our model, these uncertainties are predominantly determined by the uncertainties in the lifetime risk of developing breast cancer, and also in the preclinical growth model parameter, as indicated by the sensitivity analysis of the main model output. As there is a lot of international variability in the uptake of prevention strategies in *BRCA1* and *BRCA2* mutation carriers, and as their effect is under debate, this was not included in our model (Metcalf *et al*, 2007; Fakkert *et al*, 2012).

The strategies we evaluated for screening women with *BRCA1* or *BRCA2* mutations were the recommended strategies in the Netherlands, in the United Kingdom and in the United States. As these strategies are partly based on evidence and partly on expert opinions, recommendations are continuously being adapted to new data. For example, in a recent online publication supplementing the NICE guidelines, it was proposed to intensify frequency of mammography screening in the United Kingdom for age 50–60 years in some high-risk groups ([www.icr.ac.uk](http://www.icr.ac.uk)). Here we have presented information to further support tailoring screening recommendations for women with *BRCA1* and *BRCA2* mutations.

In conclusion, from a cost-effectiveness perspective, the Dutch screening strategy is preferred in the Netherlands for the screening of high-risk women. The highly intensive US strategy does not seem to be a cost-effective option in the Dutch situation. The less-effective UK strategy would save relatively little in costs and result in life-years lost.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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